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Event-related potential measures of gap detection threshold during natural sleep

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HIGHLIGHTS

- Event-related potentials were used to provide an estimate of the gap detection threshold during sleep.
- Gap detection thresholds could be accurately estimated while the subject was awake using the amplitude of N1, peaking at about 100 ms and also during stage N2 of sleep using the amplitude of P2, peaking at about 200 ms.
- Only larger suprathreshold gaps were able to elicit N1 and P2 during REM sleep.

ABSTRACT

Objective: The minimum time interval between two stimuli that can be reliably detected is called the gap detection threshold. The present study examines whether an unconscious state, natural sleep affects the gap detection threshold.
Methods: Event-related potentials were recorded in 10 young adults while awake and during all-night sleep to provide an objective estimate of this threshold. These subjects were presented with 2, 4, 8 or 16 ms gaps occurring in 1.5 duration white noise.
Results: During wakefulness, a significant N1 was elicited for the 8 and 16 ms gaps. N1 was difficult to observe during stage N2 sleep, even for the longest gap. A large P2 was however elicited and was significant for the 8 and 16 ms gaps. Also, a later, very large N350 was elicited by the 16 ms gap. An N1 and P2 was significant only for the 16 ms gap during REM sleep.
Significance: ERPs to gaps occurring in noise segments can therefore be successfully elicited during natural sleep. The gap detection threshold is similar in the waking and sleeping states.

1. Introduction

1.1. Gap detection thresholds

Temporal resolution refers to the ability to detect rapid changes in a sound envelope, an ability thought to be critical for the perception of speech and the localization of sound. Temporal resolution is often studied using gap detection methods in which a silent period (or "gap") is inserted in a long duration auditory stimulus. The minimum time interval between two stimuli that can be reliably detected provides a measure of the gap detection threshold. There is general agreement that normal-hearing young adults can detect 3–5 ms gaps in moderately loud continuous white noise although this is influenced by a number of factors including the intensity and frequency of the stimulus in which the gap is inserted and the duration of this stimulus (Moore, 1997; He et al., 1999; Samelli and Schochat, 2008). Temporal processing is poorer in children with language delay and in those with aphasia, dyslexia or central auditory processing disorder (Farmer and Klein, 1995; Phillips et al., 2010). There may also be a decline in gap detection threshold in the elderly (Schneider and Hamstra, 1999; Ross et al., 2010; Harris et al., 2010, 2012; Lister et al., 2011).

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The usual gap detection testing procedures require the active participation and co-operation of the observer. Certain individuals, for example, infants, young children and the senile may either be unable or unwilling to continually focus attention on the detection task during the relatively long testing interval. In these cases, event-related potential (ERP) procedures can be used to obtain a so-called "objective" estimate of gap detection. In young adults, the presentation of a gap occurring in a long duration stimulus elicits a negative component, N1, peaking at about 100 ms after the onset of the gap (offset of the stimulus), followed by a smaller amplitude positive component, P2, peaking at about 180–200 ms (Michalewski et al., 2005; Pratt et al., 2005, 2007; Lister et al., 2007; Ross et al., 2010; Palmer and Musiek, 2013). The amplitude of N1 gradually decreases as the duration of the gap decreases and a reliable N1 can still be elicited by gaps that exceed 5 ms (Pratt et al., 2005; Atcherson et al., 2009; He et al., 2012).

1.2. The effects of sleep

In spite of the potential benefit of ERP methods for the objective detection of gap thresholds, they have not often been employed in clinical populations. This is because the recording of ERPs from wakeful participants also requires extensive co-operation for relatively long periods of time in order to reduce movement and blinking artifact. This is often not possible in the very cases for whom objective ERP measures of gap detection might be most useful. An ideal setting in which ERPs can be recorded for long periods of time without concern for artifact is during natural sleep. Long latency ERPs such as N1 and P2 are however markedly affected by sleep (see Campbell and Colrain, 2002; Colrain and Campbell, 2007 and Czisch et al., 2009 for reviews). Campbell and Macdonald (2011) recorded ERPs to 20 ms gaps occurring in 1.5 s duration white noise segments during all-night sleep. The intensity of the white noise segment was either 60 or 80 dB peak Sound Pressure Level (SPL). N1 was at or near baseline level during non-REM (NREM) sleep and much attenuated during REM sleep compared to the waking state. A later P2 was however much larger during NREM and somewhat larger during REM sleep compared to that recorded in the waking state. Thus, although the morphology of the N1 and P2 components did differ between the waking and sleeping states, a distinct gap-elicited neural response remained visible. In addition, a very large amplitude negativity, peaking at about 350 (the "N350"), was visible following the presentation of the gap occurring the 80 dB SPL segment.

1.3. The purpose of this study

Although Campbell and Macdonald (2011) have demonstrated that gap-elicited ERPs are clearly discernible in the sleeping subject when a long supra-threshold duration gap is embedded in an auditory stimulus, it is not known whether this would be the case as the duration of the gap approaches threshold width. The present study varied the duration of the gap from below threshold (2 ms) to well above threshold levels (16 ms).

2. Methods

2.1. Subjects

Twelve self-reported good sleepers (6 females) between the ages of 21 and 25 years spent a single night in the sleep lab. None had a history of neurological or psychiatric disorder. Normal hearing was verified to be within 15 dB ISO for 500, 1000, 2000 and 4000 Hz frequencies. Subjects were asked to refrain from caffeine and alcohol use in the 24 h prior to testing. Subjects signed a consent form and received an honorarium for participation in this study. The study was conducted according to the guidelines of the Canadian Tri-Council (Health, Natural and Social Sciences) on ethical conduct involving human subjects. Two of the subjects were frequently awakened by the stimulus and their data were thus rejected from further analyses.

2.2. Stimuli and procedure

A 70 dB peak SPL 1500 ms duration (rise-and-fall 5 ms) auditory white noise segment was presented monaurally to the right ear through EAR-3A foam insert earphones. The spectral content of the noise was flat (within 10 dB) across the 100–10,000 Hz frequency range. Equally probable and randomly occurring 2, 4, 8 or 16 ms gaps were introduced 1000 ms after stimulus onset. The gap had a square onset and offset. The noise segment was presented every 3 s. A total of 200 stimuli were presented within a block lasting 10 min.

The waking data were collected from 21:00–23:00. In the waking state, subjects were asked to read a book or magazine of their choice and ignore the auditory stimuli. Horizontal eye movements were monitored to assure compliance with these instructions. After completion of the physiological recording, subjects were engaged in a behavioural task in which they were asked to signal their detection of the gap by button pressing. On 20% of trials, no gap was presented while a 2, 4, 8 or 16 ms gap was presented with equal probability on the remaining 80% of trials. Order of presentation of the different duration gaps was randomized. In total, 100 trials were presented (i.e., 20 each of the 0, 2, 4 8 and 16 ms gaps). Subjects were permitted to sleep at 23:30.

At least 3 blocks of stimuli were presented in definitive wakefulness, stages N2 (former stage 2) and REM of sleep. Sleep stages were classified in real-time by an experienced sleep researcher. Only blocks in which the subject did not change sleep stage (i.e., the entire block consisted of a homogenous stage of sleep) were retained for further analysis. If there was evidence of arousal or movement, stimulus presentation was paused and only resumed again if the subject returned to the same stage of sleep. If a change of sleep stage was observed within the block, all data were rejected. The sleep stage scoring was later verified by other scorers (see details below). Time between stimulus presentation blocks was approximately 20 min. There were sufficient data to permit the analysis of at least 3 blocks of data for all subjects in stage N2 and for 8 of the subjects in stage REM. Two blocks of stimuli were analyzed during stage REM for the other 2 subjects. There were insufficient data for the analysis of the data during stage N3 (former stages 3 and 4). Previous studies have however indicated that the N1 and P2 components vary minimally between stages N2 and N3.

2.3. Physiological recordings

The EEG was recorded from Fz, Cz, Pz and Oz using silver/silver chloride electrodes and referenced to the tip of the nose. The occipital electrode placement was employed to assist in the determination of sleep onset. Vertical eye movements and blinks were recorded from electrodes placed at the infra- and supra-orbital ridges of the left eye. A horizontal EOG was recorded from electrodes placed at the outer canthus of each eye. The ground electrode was located on the forehead. Inter-electrode impedances were below 2 kOhms for the EEG electrodes and below 5 kOhms for the EOG electrodes. The physiological signals were amplified with a bandpass of 0.03–35 Hz. The 0.03 Hz high-pass filter corresponded to a time constant of 5 s. The physiological signals were continuously digitized at a 256 Hz sampling rate and stored on hard disk for later off-line analyses.

2.4. Data analysis

Eye movement and blink artifact occurring in the waking state were corrected using an algorithm operating in the frequency domain (Woestenburg et al., 1983). Eye movements during REM sleep are less problematic. This is because they occur relatively infrequently and they occur at random, hence are not time-locked to the stimulus.

Following the data collection, the EEG was reclassified off-line by two experienced scorers into different stages (Wake, stage N2, stage REM), according to the American Academy of Sleep Medicine (AASM) task force criteria (Silber et al., 2007). Both scorers were blind to the real-time staging of the EEG. A 16 s epoch was used for sleep staging. This epoch is shorter than that used in most sleep studies in order to increase precision of staging. In cases of stage ambiguity (i.e., when the scorers disagreed), the entire block of data was excluded from further analysis. In actual fact, disagreement was exceedingly rare. This is because stimuli were only presented during definitive (unambiguous) stages of sleep; further, when a change of stage occurred, the entire block of data was rejected. Standard sleep recording procedures also often include a sub-mentalis EMG channel to resolve possible ambiguity about the classification of REM sleep. EMG was not recorded in the present study because in cases of ambiguity, the entire block of data was rejected. The continuous EEG was then segmented into single trials beginning 100 ms before the onset of the gap and continuing for 600 ms following it. The single trials were then baseline-corrected, filtered (1–20 Hz bandpass using a zero phase shift filter operating in the frequency domain)[1], sorted and averaged according to electrode site, the duration of the gap, and stage of sleep. Data across repetitions were collapsed, to improve the signal-to-noise ratio of the ERP. Segments in which the EEG exceeded ±100 μV in the waking state were considered to be abnormal and therefore rejected. During sleep, segments in which the EEG exceeded ±150 μV were rejected. Similar rejection criteria have been employed in many sleep studies. The rejection of EEG that exceeded ±150 μV during sleep thus allowed for the inclusion of the already filtered high amplitude slow wave (delta) EEG activity in the single segments.

ERPs were measured relative to the average of all data points within the pre-stimulus baseline period. For some of the ERP components, clear peaks were difficult to identify in individual waveforms, even when elicited by the widest gap. Data were therefore quantified using mean amplitudes during a specified latency window instead of maximum peak detection methods. Based on the grand averages (the average of all subjects' averages), the peak latencies of N1 (occurring from 80 to 140 ms), P2 (occurring from 170 to 250 ms) and N350 (occurring from 300 to 400 ms) were determined for each gap duration and each stage of sleep. All data points within ±20 ms of the peak latency of these components were then averaged in the individual subject waveforms (see Picton et al., 2000 for discussion of this issue). N1, P2 and N350 were quantified at Cz, the sites at which their amplitude was largest. The mean amplitude value of the N1, P2 and N350 components served as dependent measures. A 2-way ANOVA with repeated measures on gap Width (2, 4, 8, or 16 ms) and Stage of sleep (awake, stage N2 and REM) was performed for each component.

A critical question in this experiment was whether an ERP component would be elicited especially by short duration gaps in the sleeping subject. The usual ANOVA statistical procedure cannot be used to determine if an ERP component was actually elicited because this procedure serves to determine whether *differences* among stages or among stimuli were significant. Confidence intervals were therefore also computed for each gap duration within wakefulness and stages N2 and REM of sleep to verify the presence of an N1, P2, or N350. This procedure determined if the amplitude of each ERP deflection was significantly different from the zero voltage pre-baseline level. Upper and lower confidence limits were thus computed. In the case of the negative deflections (N1, N350), if the upper limit was greater than 0 μV (i.e., was positive-going), the component was not considered to be present. In the case of the positive deflection, P2, presence of the component required the lower limit to be above 0 μV. Because the directionality of each ERP deflection was predicted, a liberal one-tailed test of significance ($p < .05$) was applied to the confidence intervals.

3. Results

3.1. Performance data

The mean false detection rate of the trials in which no gap occurred was .08 (SD = .03). On the other hand, the detection rate for the 8 and 16 ms durations gaps was .70 and .94 respectively (SDs = .11 and .04 respectively). The mean detection rate dropped to .42 (SD = .08) for the 4 ms gap and dropped even farther to .18 for the 2 ms gap (SD = .16).

3.2. Physiological data

Fig. 1 presents the grand averaged ERPs at Fz, Cz and Pz for the wide, 16 ms duration gap during the waking and sleeping states. The ERPs following the onset of both the white noise burst and the gap in the noise are illustrated. As may be observed, in the waking state (left column), a large amplitude N1 maximal over centro-frontal areas of the scalp was visible at about 110 ms after onset of the gap. The N1 was followed by a smaller amplitude P2, peaking at about 180 ms. Sleep had a dramatic effect on ERP morphology. During NREM sleep stage N2 (middle column), the N1

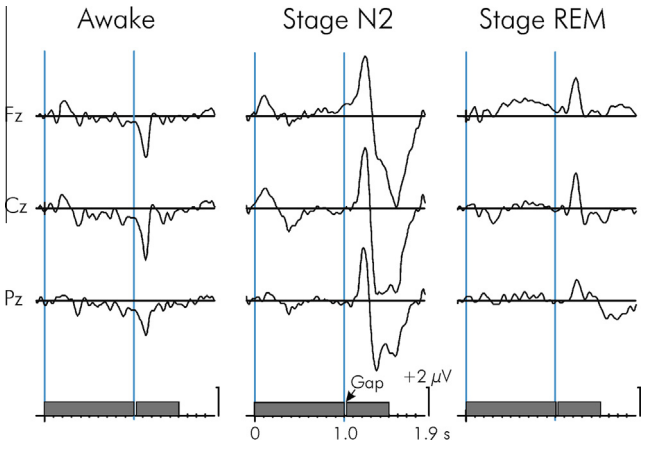

Fig. 1. Effects of sleep on the detection of a 16 ms gap occurring in a 70 dB SPL white noise segment. The grand-averaged ERPs within the waking state and during stages N2 and REM of sleep are illustrated. In this figure and in Fig. 2, positivity at the scalp relative to the nose reference is indicated by an upward deflection. Subjects were presented with a 1.5 s burst of white noise. A gap was introduced after 1 s. In this example, gap width is 16 s. The ERPs following the onset of the white noise and the onset of the gap are illustrated. When the subject was awake, the 16 ms gap elicited a large amplitude fronto-central maximum N1, peaking at about 110 ms, followed by a smaller amplitude P2, peaking at about 180 ms. Sleep caused very large changes to the morphology of the gap-elicited ERP. N1 was difficult to observe during stage N2 of NREM sleep. P2 was however much larger in amplitude than in the waking state., N1 returned to about 15% of its waking amplitude during stage REM sleep. A very large amplitude N350, maximum over the central site was apparent in stage N2. It was not elicited in the waking state and was much reduced in amplitude during stage REM sleep.

[1] A 1 Hz low filter is often used in ERP sleep studies to attenuate high amplitude delta activity, prominent during NREM sleep. This will however somewhat attenuate the slower frequency N350 component.

component was at or near baseline while the amplitude of P2 increased markedly. During REM sleep (right column), a small amplitude N1 was visible and followed by a more prominent P2 than that elicited during the waking state. A very large (about 15 μV) central maximum N350 was elicited during stage N2. The N350 was much attenuated during stage REM sleep, and was absent in the waking state.

Fig. 2 illustrates the effects of decreasing the width of the gap on the ERP waveforms elicited during the waking state and each stage of sleep. The mean N1, P2 and N350 amplitude data for the different gap widths within the waking and sleeping states are presented in Table 1.

3.2.1. N1 waveform

N1 was maximum over centro-frontal areas of the scalp. The repeated-measures ANOVA performed on mean Cz amplitude values for N1 resulted in a significant gap Width x Stage interaction, $F(6,54) = 3.12$, $p < .01$. Simple main effects testing was used to isolate the source of the interaction. The N1 elicited during the waking state was significantly larger in amplitude than that observed in any of the stages of sleep (N2 and REM) for the 8 and 16 ms duration gaps. The waking–sleeping N1 amplitude differences were not significant following presentation of either the 4 or the 2 ms duration gaps. The effects of the duration of the gap were also isolated within each sleep stage. In the waking state, a significant effect of gap duration was found. The amplitude of N1 gradually declined in amplitude as the width of the gap narrowed. The manipulation of the duration of the gap did not have a significant effect on N1 during either stages N2 or REM sleep.

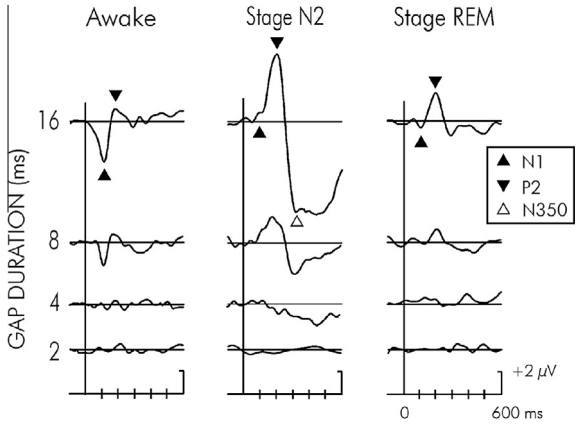

Fig. 2. Grand averaged ERPs as a function of gap width and stage of sleep. These data are from the Cz electrode placement. In the waking state, as the width of the gap narrowed from 16 to 8 ms, the amplitude of N1 declined. Only a small and nonsignificant N1 is apparent for the 4 ms gap. During stage N2 of sleep, an N1 is not apparent, regardless of the width of the gap. However, a large P2 is visible for the wider 8 and 16 ms gaps. A very large amplitude N350 is also visible for the 8 and 16 ms gaps. During REM sleep, only the widest 16 ms occurring in the white noise segment was able to elicit a significant N1and P2.

Confidence interval analyses indicated that in the waking state, a significant N1 was elicited for the 8 and 16 ms gaps, but not for the 2 or 4 ms gaps. On the other hand, during stage N2 sleep, none of the stimuli elicited a significant N1, not even when the widest, 16 ms gap, occurred. During REM sleep, only the 16 ms gap elicited a significant N1.

3.2.2. P2 waveform

P2 was maximum at Cz. A significant gap Width x Stage interaction was obtained for the mean amplitude values in the P2 time window, $F(6,54) = 2.54$, $p < .05$. P2 was significantly larger during stage N2 sleep than during either the waking state or REM sleep for the stimuli containing either 16 or 8 ms duration gaps. The P2 elicited during REM sleep was significantly larger than that observed in the waking state, but only for the widest 16 ms gap. Differences for the narrower 4 and 2 ms gaps were not significant between waking and sleeping states. The decrease in the amplitude of P2 with narrowing gap duration was significant in both wakefulness and during sleep (stages N2 and REM).

Confidence interval analyses showed that during wakefulness, a significant P2 was again apparent only for the 8 and 16 ms duration gaps. Its amplitude was not significantly different from the 0 μV pre-stimulus baseline level for either the 2 or 4 ms gaps. During stage N2, a significant P2 was also elicited by both the 8 and 16 ms duration gaps. Only the widest 16 ms gap elicited a significant P2 during stage REM sleep.

3.2.3. N350 waveform

N350 was also maximum at Cz. The ANOVA again revealed a significant gap Width x Stage interaction, $F(6,54) = 4.60$, $p < .01$. N350 was significantly larger in stage N2 than in either wakefulness or stage REM for the 8 and 16 ms gaps, but not for the narrower 2 and 4 ms gaps. N350 was significantly larger in stage REM compared to the waking state but only for the widest 16 ms gap.

Confidence interval testing revealed a significant N350 for only the widest gaps (16 and 8 ms) during stage N2 sleep. A small N350 was apparent during stage REM when elicited by the 16 ms duration gap, but it did not significantly differ from the zero voltage pre-stimulus baseline level. A significant N350 was not apparent in the waking state, even for the widest gap.

4. Discussion

Previous research has indicated that ERPs can be reliably elicited by 5 ms gaps inserted in continuous white noise during the

Table 1
Mean amplitude (SDs in parentheses) of N1, P2 and N350 during the waking state and during NREM and REM sleep.

Stage	Width (ms)	N1	P2	N350
Awake	16	−6.66 (3.17)	2.04 (1.86)	−0.92 (3.23)
	8	−3.98 (1.87)	1.47 (1.23)	−1.77 (3.76)
	4	0.23 (1.63)	1.48 (2.11)	0.05 (1.16)
	2	0.81 (1.35)	0.42 (1.74)	1.04 (1.12)
NREM	16	1.66 (1.45)	10.03 (4.53)	−13.10 (5.88)
	8	1.82 (1.75)	3.83 (1.90)	−4.52 (2.24)
	4	0.54 (0.88)	−0.60 (0.85)	−1.78 (2.65)
	2	−1.04 (1.31)	−0.68 (0.82)	0.11 (0.61)
REM	16	−1.10 (0.58)	5.71 (2.37)	−2.46 (1.74)
	8	−0.33 (1.16)	2.60 (1.26)	−0.91 (1.02)
	4	0.86 (1.08)	0.85 (1.29)	−0.28 (1.85)
	2	0.03 (0.77)	−0.12 (1.16)	0.82 (1.61)

waking state. The present study examined whether these objective ERP threshold estimates can also be obtained during natural sleep. In the present study, results of the performance task confirm that gaps having a duration as short as 8 ms inserted in moderately intense discrete white noise stimuli are easily behaviourally detected (detection rate of .70); and this result was not achieved by the adoption of a liberal strategy. When a gap was not present in the noise segment, the false detection rate was very low (.08). Similarly, detection rates of very narrow, 2 ms gaps were below .20. The mean detection rate for the 4 ms gap in the present study was only .42, but the gaps were inserted in relatively short duration discrete white noise segments. The gap detection threshold is higher when gaps are inserted in short duration stimuli compared to continuous stimuli (Pratt et al., 2007). Unfortunately, it is difficult to employ very long or continuous duration stimuli in sleep studies because they may cause arousals or awakenings.

As expected, the manipulation of the duration of the gap was successful in causing variation in ERP morphology in the waking state. The amplitude of N1 gradually decreased as the duration of the gap was shortened, replicating the findings of Pratt et al. (2005). Although an N1 was still visible in the grand averaged data following the insertion of the 4 ms gap (see Fig. 2), it could not be reliably detected in the background EEG of individual subjects. The waking N1 data therefore closely mirrored the behavioural performance data. In contrast, only a small amplitude P2 was elicited in the waking state and confidence interval testing indicated that it was significantly different from the zero voltage baseline only for the widest, 16 ms gap.

It is well known that sleep has a very large effect on the N1–P2 morphology, elicited by the onset of brief duration stimuli. The amplitude of N1 gradually declines at sleep onset, reaching baseline levels during NREM sleep but does return to 15–40% of its waking amplitude during REM sleep. In contrast, the amplitude of P2 is typically larger during sleep, in particular during NREM, than during wakefulness. Some auditory stimuli can also elicit ERPs that are only observed during sleep, such as the N350 which is larger during NREM compared to REM sleep. These sleep-related changes in ERP morphology were also observed in the present study when elicited by a gap inserted in white noise. During NREM sleep, N1 was difficult to discern even when elicited by the long 16 ms gap whereas during REM sleep, the 16 ms gap evoked a small but significant N1. By contrast, a large P2 was elicited by the 16 ms gap in both stage N2 and REM. The amplitude of P2 gradually decreased during sleep as the duration of the gap decreased. During stage N2 sleep, a significant P2 was elicited by the 8 ms gap, but not for either the 4 or 2 ms gaps. Thus, although active processing is largely inhibited during sleep (in order to prevent consciousness of the external environment), passive detection of the supra-threshold duration gaps occurring in the noise segments was still apparent. Indeed, objective ERP estimates of the gap duration threshold within stage N2 sleep closely approximated those observed in the waking state.

During stage N2 sleep, a very large amplitude late negativity, the N350, was also apparent following the occurrence of the 16 ms gap. The amplitude of the N350 was much reduced for the 8 ms gap in stage N2 sleep and during REM sleep. Colrain et al. (2000) suggest that the N350 reflects an inhibitory process, preventing obtrusive stimuli from disturbing sleep. It is well-known, for example, that the amplitude of N350 increases as the intensity of a short duration auditory stimulus increases (Bastien and Campbell, 1992; Macdonald et al., 2008; Muller-Gass and Campbell, 2010).

The use of objective gap detection methods is becoming increasingly important in the applied and clinical settings. Objective ERP estimates of gap duration threshold recorded during the waking state do however require the active participation and co-operation of the patient. This may not always be possible especially with certain populations such as infants, young children and the senile. The present study indicates that objective ERP estimates of gap duration thresholds can be as accurately estimated during sleep, in particular during stage N2, as in wakefulness. The results suggest that gap threshold testing of these populations could thus be performed while they are sedated or during sleep. A limitation of this proposed methodology is however that testing time may need to be long to obtain an objective estimate of the duration threshold of gap detection. Testing time could be significantly reduced if an overall evaluation of gap detection ability is sufficient because the N350 component could be employed for this purpose. The signal-to-noise ratio is particularly high for the N350 and thus, only a small number of stimulus presentations would be required for it to emerge in the background EEG of sleep. Presumably, it could be recorded even during brief naps. While the N350 is easily observed when a wide duration gap is inserted in a stimulus, this is not the case for shorter but above threshold duration gaps.

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